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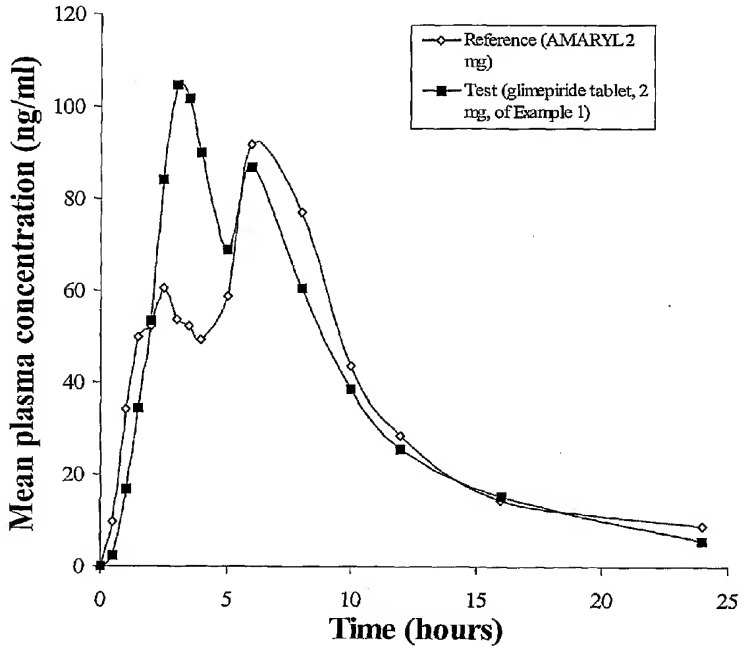

(57) Abstract: The present invention provides a pharmaceutical composition of glimepiride comprising milled glimepiride or its mixture with one or more pharmaceutically acceptable excipients wherein the milling of glimepiride and the pharmaceutically acceptable excipients is optimized such that the pharmaceutical composition obtained upon using the milled mixture is bioequivalent with pharmaceutical composition of glimepiride commercially available in the United States of America in November 2001.

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PHARMACEUTICAL COMPOSITION FOR TREATMENT OF DIABETES MELLITUS

FIELD OF THE INVENTION

The present invention provides a pharmaceutical composition for the treatment of diabetes mellitus and conditions associated with diabetes mellitus. Particularly, the present invention provides a pharmaceutical composition comprising glimepiride.

BACKGROUND OF THE INVENTION

Non-insulin dependent diabetes mellitus (NIDDM), also known as maturity-onset diabetes or diabetes mellitus type 2, is a frequent metabolic disease and the main cause of hyperglycemia. It is a heterogeneous disease with complex, unclarified metabolic aspects. Insulin secretion may appear normal or even excessive, but it is insufficient to compensate for insulin resistance. The disease is characterized by three main abnormalities of metabolism contributing to hyperglycemia. These include the partial or complete decrease in insulin secretion, resistance of the peripheral tissues to insulin and increased hepatic production of glucose in fasting conditions. Diet and physical exercise cause a reduction in insulin-resistance and lead to an improvement in the pancreas deficit over a period of time.

When these provisions are not sufficient, a pharmacological agent needs to be taken for control of hyperglycemia. The treatment goal of NIDDM is to normalize blood-glucose level in an attempt to prevent or reduce complications that may arise due to chronic hyperglycemia. The effect of regular exercise supplementing diet in patients with NIDDM causes a reduction in insulin-resistance and leads to an improvement in the pancreas deficit over a period of time. When these provisions are not sufficient, a pharmacological agent needs to be taken for control of hyperglycemia. Oral medications work either to reduce the body's resistance to its own insulin, or work to increase insulin secretion to meet the demand. Sulfonylureas and biguanides have been used in oral antidiabetic therapy. Other classes of oral antidiabetic agents include the alpha-glucosidase inhibitors, aldose reductase inhibitors, thiazolidinediones, insulin secretagogues and others. The use of these classes of compounds in monotherapy has been effective in obtaining a glycometabolic control in diabetic patients.

The mechanism of action of sulfonyl ureas involves lowering of blood glucose concentration mainly by stimulating release of endogenous insulin from beta cells of the pancreas, and thus they act as hypoglycemic agents. The sulfonyl ureas are used as an adjunct to diet for the management

of non-insulin dependent diabetes mellitus in patients whose hyperglycemia cannot be controlled by diet alone.

Glimepiride is an oral blood-glucose lowering drug of the sulfonylurea class. Chemically, glimepiride is N-(4-[2-(3,4-dimethyl-2-oxo-3-pyrroline-1-carboxamido)-ethyl]-benzenesulfonyl)-N'-4-methyl-cyclohexyl-urea or 1-[[p-[2-(3-ethyl-4-methyl-2-oxo-3-pyrroline-1-carboxamido) ethyl]phenyl]-sulfonyl]-3-(trans-4-methylcyclohexyl)urea. It is indicated as an adjunct to diet and exercise to lower the blood glucose in patients with non-insulin dependent (type-II) diabetes mellitus (NIDDM) whose hyperglycemia cannot be controlled by diet and exercise alone. The primary mechanism of action of glimepiride in lowering blood glucose appears to be dependent on stimulating the release of insulin from functioning pancreatic beta cells. In addition, extrapancreatic effects may also play a role in the activity of glimepiride. The usual starting dose of glimepiride as initial therapy is 1-2 mg once daily, administered with breakfast or the first main meal. The maximum starting dose should be no more than 2 mg. The usual maintenance dose is 1 to 4 mg once daily.

AMARYL® is the currently commercially available pharmaceutical composition of glimepiride marketed in the United States of America by Hoechst-Roussel (Aventis). It is available as tablets in 1mg, 2mg and 4mg strengths, all strengths being approved by USFDA since November 30, 1995. AMARYL® is indicated as an adjunct to diet and exercise to lower the blood glucose in patients with type II diabetes mellitus.

United States patent no. 4,379,785 ('785 patent) claims sulfonyl ureas, particularly N-(4-[2-(3,4-dimethyl-2-oxo-3-pyrroline-1-carboxamido)-ethyl]-benzenesulfonyl)-N'-4-methyl-cyclohexyl-urea or glimepiride and a pharmaceutical composition for lowering the blood sugar level in a patient suffering from diabetes, which comprises orally administering a hypoglycemically effective amount of the sulfonyl urea or salt thereof in combination with a pharmaceutically acceptable carrier. The patent discloses that suitable medicament formulations of the drug are preferably tablets containing the usual carriers and auxiliaries such as talc, starch, lactose or magnesium stearate, in addition to the sulfonyl ureas or the salts thereof. The '785 patent discloses that it may be advantageous to use the active substance(s) in ground or finely dispersed form. However, neither does it provide any details on such ground substances, nor does it describe the use of such ground active substances for enhancing or improving bioavailability of glimepiride.

Canadian patent no. 2,173,366 relates to a simple process for dissolving sparingly soluble sulfonylurea derivatives under mild conditions. The patent claims a highly effective preparation of sulphonylurea derivatives which releases the active substance rapidly or in a controlled manner, characterized in that it contains one or more sulphonylurea derivative(s) as active substance(s), alcohol, one or more polyol(s), with the exception of polyethylene glycol, and/or one or more sugar alcohol(s), previously dissolved in water or an alcohol/water mixture, an alkaline substance and optionally further pharmaceutically active substances. However, the patent does not disclose or exemplify immediate release solid dosage forms of glimepiride wherein the particle size of glimepiride is reduced to enhance or improve its bioavailability.

United States patent application no 20030129250A1 relates to particulate compositions for improving solubility of poorly soluble agents. The application claims a composition comprising amorphous, hollow particles comprising regions of a poorly soluble agent embedded within the walls of said particles wherein the dissolution rate enhancement of the particles is between 2-fold and about 25-fold compared to the agent in bulk form. The particles of the invention are produced by spray-drying a dilute solution of the active agent, optionally with one or more excipients. The patent application in fact refers to milling as a problematic solution responsible for unwanted polymorphic transition, agglomeration, poor flowability and poor wettability.

We have surprisingly found that milling glimepiride or its mixture with one or more pharmaceutically acceptable excipients, under controlled conditions, provides dosage forms which are bioequivalent with currently commercially available dosage forms of glimepiride, while not causing any problems heretofore mentioned in the prior art.

OBJECT OF THE INVENTION

It is an object of the present invention to provide a pharmaceutical composition of glimepiride comprising milled glimepiride or its mixture with one or more pharmaceutically acceptable excipients wherein the milling of glimepiride and the pharmaceutically acceptable excipients is optimized such that the pharmaceutical composition obtained upon using the milled mixture is bioequivalent with pharmaceutical composition of glimepiride commercially available in the United States of America in November 2001.

SUMMARY OF THE INVENTION

The present invention provides a pharmaceutical composition of glimepiride comprising milled glimepiride or its mixture with one or more pharmaceutically acceptable excipients wherein the milling of glimepiride and the pharmaceutically acceptable excipients is optimized such that the pharmaceutical composition obtained upon using the milled mixture is bioequivalent with pharmaceutical composition of glimepiride commercially available in the United States of America in November 2001.

The present invention further provides a pharmaceutical composition of glimepiride comprising milled glimepiride or its mixture with one or more pharmaceutically acceptable excipients wherein the milling of glimepiride or its mixture with one or more pharmaceutically acceptable excipients is optimized such that the pharmaceutical composition obtained upon using the milled mixture has the following dissolution profile –

(i) Not less than 30% and not more than 75% of glimepiride is released after 10 minutes,

(ii) Not less than 60% and not more than 90% of glimepiride is released after 30 minutes, and

(iii) More than 80% of glimepiride is released after 60 minutes,

when tested in United States Pharmacopoeia type II dissolution apparatus at 75 rpm at 37 ± 0.5^{0}C using low ionic strength buffer, pH 6.8.

BRIEF DESCRIPTION OF THE DRAWING

Figure 1 shows the plasma concentration vs time profile obtained upon administration of the pharmaceutical composition of example 1, in comparison to that obtained for the commercially available glimepiride tablet, AMARYL®.

DETAILED DESCRIPTION OF THE INVENTION

The present invention provides a pharmaceutical composition of glimepiride comprising milled glimepiride or its mixture with one or more pharmaceutically acceptable excipients wherein the milling of glimepiride and the pharmaceutically acceptable excipients is optimized such that the pharmaceutical composition obtained upon using the milled mixture is bioequivalent with pharmaceutical composition of glimepiride commercially available in the United States of America in November 2001.

The pharmaceutical composition of the present invention provides blood plasma levels of glimepiride that are effective in the treatment of diabetes mellitus and conditions associated with diabetes mellitus, while being bioequivalent with pharmaceutical composition of glimepiride commercially available in the United States of America in November 2001.

The pharmaceutical composition of the present invention may have a lower rate of dissolution than the pharmaceutical composition of glimepiride commercially available in the United States of America in November 2001 when tested in United States Pharmacopoeia type II dissolution apparatus at 75 rpm at 37 ± 0.5^{0}C using low ionic strength buffer, pH 6.8. Nevertheless, the pharmaceutical composition of the present invention when tested in human subjects is found to be bioequivalent with AMARYL® tablets. For example, when tested under the above stated dissolution test conditions, AMARYL® tablets show release of at least 80% in 10 minutes, while the pharmaceutical composition of the present invention may release less than 60% in 10 minutes.

Accordingly, the present invention provides a pharmaceutical composition of glimepiride comprising milled glimepiride or its mixture with one or more pharmaceutically acceptable excipients wherein the milling of glimepiride or its mixture with one or more pharmaceutically acceptable excipients is optimized such that the pharmaceutical composition obtained upon using the milled mixture has the following dissolution profile –

(i) Not less than 30% and not more than 75% of glimepiride is released after 10 minutes,

(ii) Not less than 60% and not more than 90% of glimepiride is released after 30 minutes, and

(iii) More than 80% of glimepiride is released after 60 minutes,

when tested in United States Pharmacopoeia type II dissolution apparatus at 75 rpm at 37 ± 0.5^{0}C using low ionic strength buffer, pH 6.8.

Glimepiride is used in the present invention in an amount ranging from about 0.5mg to about 15mg, preferably from about 1mg to about 10mg. Glimepiride or its mixture with one or more pharmaceutically acceptable excipient(s) is provided to the milling chamber of a mill. Non-limiting examples of such mills for grinding the pre-mix may be selected from a rotary mill, high vibration mill, ball mill, colloid mill, roller mill, mortar mill, planetary mill and the like. The milling procedure adopted may be dry milling using glimepiride and one or more excipients, or it

may be wet milling using an aqueous solvent, one or more organic solvents, or a mixture thereof. The process of milling glimepiride or its mixture with one or more pharmaceutically acceptable excipient(s) is optimized such that the mixture obtained upon milling, when converted to a pharmaceutical composition by conventional means, provides plasma levels of glimepiride equivalent to those obtained using commercially available compositions of glimepiride. The optimization of the milling process involves individual optimization of several parameters such as the mill used, type of milling used, i.e. wet or dry milling, time of milling, speed of the mill, and optimization of a combination of all these parameters.

In one embodiment of the present invention, the pharmaceutical composition is obtained by milling glimepiride or its mixture with one or more pharmaceutically acceptable excipient(s) in a ball mill for a period of eight hours at a speed of 40 rpm, and converting the mixture thus obtained into a pharmaceutical composition by conventional means. The pharmaceutical composition thus obtained provides plasma concentration of glimepiride such that the composition is bioequivalent with commercially available glimepiride tablets, AMARYL®.

The pharmaceutically acceptable excipients that may be used in the present invention include disintegrants such as starch, cellulose derivatives, gums, crosslinked polymers and the like; binders such as starch, gelatin, sugars, cellulose derivatives, polyvinyl pyrrolidone and the like; lubricants such as talc, magnesium stearate, colloidal silicon dioxide, polyethylene glycol and mixtures thereof.

In a preferred embodiment, the glimepiride is milled with a binder and other pharmaceutically acceptable excipients. The binder used may be selected from the group comprising cellulose and cellulose derivatives such as methylcellulose, ethylcellulose, hydroxypropylcellulose, hydroxypropyl methylcellulose, carboxyalkyl celluloses or crosslinked carboxyalkylcelluloses and their alkali salts and the like and mixtures thereof. In a preferred embodiment, the binder used is hydroxypropyl methylcellulose in an amount ranging from about 0.5% to about 5% by weight of the pharmaceutical composition.

The present invention may be prepared by the conventional process of wet granulation, dry granulation or direct compression. In wet granulation, the milled mixture of glimepiride and pharmaceutically acceptable excipients may be granulated using an aqueous or organic solution of a suitable binder. The granules thus obtained may then be dried, lubricated and compressed.

The pharmaceutical composition of the present invention may also be prepared by dry granulation involving slugging the milled mixture of glimepiride and pharmaceutically acceptable excipients, lubricating the slugs thus obtained and compressing them to obtain the tablets. The pharmaceutical composition of the present invention may also be prepared by direct compression of the milled mixture of glimepiride and pharmaceutically acceptable excipients.

Approval of a generic version (Abbreviated New Drug Application, ANDA) of a proprietary drug (New Drug Application, NDA) by the Food and Drug Administration (FDA) requires demonstration of "chemical equivalence" (similar quantities and availability of the active ingredient in proprietary and generic formulations), and "bioequivalence" (defined by absorption parameters generally falling between 80% and 125% of those obtained with the proprietary agent under the same testing conditions). Hence a generic drug formulation to be approved by the FDA, has to be bioequivalent to the reference listed drug or the proprietary formulation. The present invention provides a pharmaceutical composition for the treatment of diabetes mellitus that releases glimepiride in a manner to provide desirable blood level profile of glimepiride that provides efficacy in the treatment of diabetes. For example, when administered as a single dose in fasted state to healthy human subjects it provides area under the plasma concentration-time curve (AUC) which is comparable to that provided by the pharmaceutical composition of glimepiride commercially available in the United States of America in November 2001. Alternatively, it provides peak plasma levels (C_{max}) that are comparable with those provided by the pharmaceutical composition of glimepiride commercially available in the United States of America in November 2001. Herein, the term comparable means that 90 percent confidence intervals for the ratio of the population geometric means between the pharmaceutical composition of the present invention and the glimepiride oral drug delivery system commercially available in the United States of America, namely Amaryl®, based on log-transformed data, is contained in the limits of 70-135 percent for AUC and C_{max}. More preferred embodiments of the present invention are bioequivalent to glimepiride drug delivery systems commercially available in the United states of America. Bioequivalence may be determined according to United States Food and Drug Administration (USFDA) guidelines and criteria.

The examples that follow are provided as illustrations and do not limit the scope of the present invention.

Example 1

The pharmaceutical composition of the present invention was obtained as per the method given below. The glimepiride and the pharmaceutically acceptable excipients are milled in a ball mill in this example.

Table 1

Sr. No	Ingredients	mg/tab	% w/w
I	*For ball milling*		
1.	Glimepiride	2.00	1.33
2.	Hydroxypropyl methylcellulose (HPMC E5 LV)	5.75	3.83
3.	Lactitol monohydrate	21.75	14.5
4.	Magnesium stearate	0.50	0.33
	Total wt of ball milled blend	30.00	20.0
II	*For Direct compression blend*		
5.	Ball milled material	30.00	20.0
6.	Hydroxypropyl methylcellulose (HPMC E5 LV)	5.00	3.33
7.	Lactitol monohydrate	114.00	76.0
8.	Magnesium stearate	1.00	0.66
	Total weight	150.00	

The ingredients to be ball milled (Ingredients were taken in amounts as shown in Table 1 above) were passed through sieve # 40 ASTM (ASTM stands for American Society for Testing and Materials), loaded into the ball mill (Kalweka Drive assembly) and milled for a period of 8 hours, at a rpm of 40. The ball milled material was then passed through sieve # 60 ASTM. This mass was mixed with lactitol monohydrate and HPMC E5LV by repeated sifting through sieve # 40 ASTM. This was further mixed thoroughly in a polybag. This blend was lubricated with magnesium stearate (presifted through sieve # 60 ASTM) in a polybag. The lubricated blend was compressed on 10 X 6.0 mm oval shaped punches on a single rotary compression machine at a target weight of 150.0 mg.

The tablets obtained by the process of the present invention and commercially available glimepiride tablets, AMARYL®, 2 mg glimepiride tablets (Lot No. 1072454; expiry: November 2003) were subjected to dissolution testing using United States Pharmacopoeia type II dissolution apparatus at 75 rpm at 37 ± 0.5°C. The dissolution medium used was 2000ml of low ionic strength buffer, pH 6.8. The results of the dissolution test are mentioned in Table 2 below.

Table 2

Time (minutes)	AMARYL® (% drug released)	Example 1 (% drug released)
5	79	20
10	86	44
15	90	61
30	93	80
60	96	87
120	97	90

Example 2

The bioavailability of the pharmaceutical composition of glimepiride (Example 1) of the present invention and that of commercially available glimepiride tablets, AMARYL® (2 mg glimepiride) were studied. A single-dose, open label, randomized, comparative and two-way crossover study, with a seven-day washout period, was undertaken for the same.

The pharmacokinetic assessment was based on the plasma levels of glimepiride measured by blood sampling. Blood samples were obtained before dosing and at the following times after administration of both the reference and test medications: 0, 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 5, 6, 8, 10, 12, 16 and 24 hours.

Twelve healthy male volunteers were enrolled for the study and eleven of them completed the two-way crossover study. The subjects were fasted overnight before dosing and for 4 hours thereafter. Drinking water was prohibited 2 hours before dosing and 2 hours thereafter, but was allowed ad lib at all other times. Standard meals were provided at 4 hours and 8 hours after dosing, and at appropriate times thereafter. Meal plans were identical for both the periods.

Subjects received a single tablet of glimepiride (2 mg, Example 1) with 240ml of drinking water at ambient temperature as the test medication, and a single oral dose of AMARYL® (2 mg) also with 240ml of drinking water at ambient temperature as the reference medication.

The plasma concentration of glimepiride was determined for samples collected at different time points and averaged over the eleven volunteers. The data is given in Table 3 below. The plasma concentration versus time profile is illustrated in Figure 1.

Table 3

Time (hrs)	Plasma concentration (ng/ml)	
	Reference (AMARYL® 2 mg)	Test (glimepiride tablet, 2 mg, Example 1)
0	0	0
0.5	9.85	2.24
1.0	34.07	16.68
1.5	49.88	34.37
2.0	52.21	53.41
2.5	60.38	83.94
3.0	53.76	104.73
3.5	52.06	101.81
4.0	49.33	90.02
5.0	58.82	68.57
6.0	91.59	86.81
8.0	76.83	60.52
10.0	43.67	38.51
12.0	28.62	25.57
16.0	14.57	15.39
24.0	8.80	5.54

The pharmacokinetic parameters calculated using the Win Nonlin software are given in Tables 4 and 5 below.

Table 4

Un-Transformed						
Parameter	**Units**	**Least Square Means**		**Ratio (%T/R)**	**90% confidence Intervals on the ratio**	
		Reference (AMARYL® 2 mg)	**Test (glimepiride tablet, 2 mg, Example 1)**		**Lower**	**Upper**
C_{max}	ng/ml	127.93	137.70	106.07	88.10	124.04
AUC_{0-t}	ng.hr/ml	834.67	851.14	101.97	94.87	109.08
AUC_{0-inf}	ng.hr/ml	869.89	896.76	99.99	91.20	108.77
T_{max}	hr	5.75	4.15	72.17	55.21	89.14

Table 5

Ln-transformed						
Parameter	**Units**	**Least Square Means**		**Ratio (%T/R)**	**90% confidence Intervals on the ratio**	
		Reference (AMARYL® 2 mg)	**Test (glimepiride tablet, 2 mg, Example 1)**		**Lower**	**Upper**
C_{max}	ng/ml	122.20	129.59	106.05	90.02	124.93
AUC_{0-t}	ng.hr/ml	803.78	831.54	103.45	96.94	110.40
AUC_{0-inf}	ng.hr/ml	857.91	877.34	102.26	94.17	111.05
T_{max}	hr	5.50	3.92	71.24	57.68	87.99

Claims:

1. A pharmaceutical composition of glimepiride comprising milled glimepiride or its mixture with one or more pharmaceutically acceptable excipients wherein the milling of glimepiride and the pharmaceutically acceptable excipients is optimized such that the pharmaceutical composition obtained upon using the milled mixture is bioequivalent with pharmaceutical composition of glimepiride commercially available in the United States of America in November 2001.

2. A pharmaceutical composition of glimepiride as in claim 1, wherein the glimepiride or its mixture with one or more pharmaceutically acceptable excipients is milled using a rotary mill, high vibration mill, ball mill, colloid mill, roller mill, mortar mill, planetary mill and the like.

3. A pharmaceutical composition of glimepiride as in claim 2, wherein the glimepiride or its mixture with one or more pharmaceutically acceptable excipients is milled using a ball mill.

4. A pharmaceutical composition of glimepiride as in claim 3, wherein the pharmaceutical composition is obtained by milling glimepiride or its mixture with one or more pharmaceutically acceptable excipient(s) in a ball mill for a period of eight hours at a speed of 40 rpm.

5. A pharmaceutical composition as in claim 1, wherein the glimepiride is used in an amount ranging from about 1mg to about 10mg.

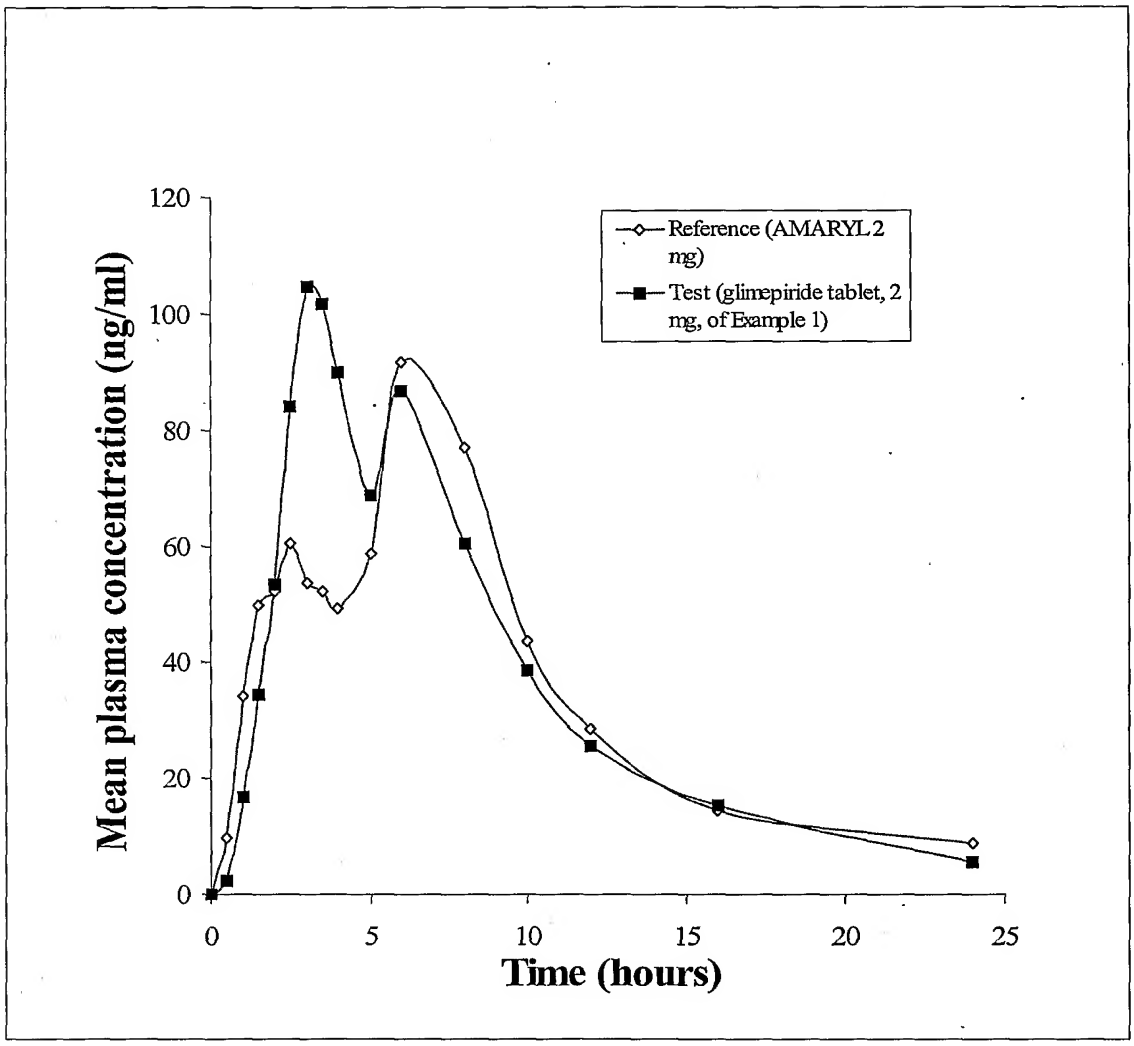
6. A pharmaceutical composition of glimepiride comprising milled glimepiride or its mixture with one or more pharmaceutically acceptable excipients wherein the milling of glimepiride or its mixture with one or more pharmaceutically acceptable excipients is optimized such that the pharmaceutical composition obtained upon using the milled mixture has the following dissolution profile –

   (i) Not less than 30% and not more than 75% of glimepiride is released after 10 minutes,

   (ii) Not less than 60% and not more than 90% of glimepiride is released after 30 minutes, and

   (iii) More than 80% of glimepiride is released after 60 minutes,

when tested in United States Pharmacopoeia type II dissolution apparatus at 75 rpm at 37 $\pm$ 0.5^{0}C using low ionic strength buffer, pH 6.8.


Mean plasma concentration (ng/ml)
120
100
80
60
40
20
0
0
5
10
15
20
25
Time (hours)
Reference (AMARYL 2 mg)
Test (glimepiride tablet, 2 mg, of Example 1)